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February 6, 1975

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Dear Paul:

As always it was a great pleasure to see you. This time it was especially good for me to hear your present views on the artificial plasmid situation. Thank you for sending me the reprint, which is returned.

I do not think we are so far apart in our concepts, though this may not be obvious from what we have put into print. I've thought about the relationship between research using human volunteers and research using artificial DNA molecules in more depth, and I will want to comment on this later, but first I think I should reply to some questions that were asked in your letter.

Parenthetically, it amuses me to think that it is likely that this correspondence is the only thing I shall ever write that might be of interest to posterity. Unfortunately, the only circumstance in which these words will be remembered is if you and your committee prove prescient, as by a catastrophe or near-miss from a man-made DNA molecule. In this game I'm in a "no-win" position--which is not too smart--since if I'm right there will be no catastrophe and the whole controversy will fade away and be forgotten. Nevertheless, on we go.

First you imply that I take a less than rigorous position because it is my ox that is geing gored. Well, it's true that I may some day want to work with a molecule of DNA I've sculpted a bit to suit my purpose, but who in biology or medicine today can say otherwise? And if a minimal or non-existant danger can be used to increase the cost, aggravation and red-tape of doing this kind of experiment, where will it stop?

I worked a little bit with human material 20 years ago, and I'm working with it now. I didn't impinge on anyone's rights or endanger their well-being when I first did it, and I don't do so now. The main difference is that now I must document this fact and spend several working days each year convincing two separate "overseers", my local human research committee and some NIH bureaucrats, that this is so. Before I had only to convince my own conscience and the blood donor.

It now appears that under the older method, when scientists were assumed to be ethical as well as honest, a few unwise human experiments were done. The system was susceptible to abuse, for reasons well-described in Dr. Ritt s' article and to prevent further abuse the government adopted, and we scientists have acquiesed to, what I will call the "permission panel" method of control. The risk of harm to the subject is clearly real, so even though the benefits may be enormous, each experiment's risk/benefit ratio must be evaluated by a panel and the upshot recorded. As every individual in our society should be protected from assault by other individuals, so must they be protected from

assault by scientists, and society is willing to pay for this protection. Much as I deplore this necessity, I accept it. The intent of my letter was only to point out its significant cost, both in actual time and money lost and in experiments not done.

You ask if I know of specific instances where good experiments were not done because of the NIH regulations concerning human research. The answer is no, except for vague rumors that all new antibiotics and contraceptives now receive their field tests in Europe and South America rather than in the U.S. to avoid red tape and delay. But I do not move in circles where I would hear about this kind of thing anyway, and I can't document even these rumors. In my own experience, as I told you, one hare-brained experiment was forestalled and twenty or more good or risk-free ones were delayed from one to three months.

So, like any rational individual, I accept regulation when the risk/benefit ratio is appreciable, as when people are the subject of the experiment. But in your case, recombinant DNA molecules are the subject of the experiment and the matter for concern. I still don't see how the risk/benefit situation differs between a man-made potential pathogen and a natural one. Why should we regulate an experimenter as though he were using human volunteers when the work he proposes to do carries no more risk than that of the infectious disease man down the hall? Is it because we have lost a few infectious disease men over the past 100 years (and made quite a few rather sick) and this historical fact is always in our collective consciousness, while no molecular biologist has yet succumbed to a creature of his own making?

If I were to write my letter over again, I would be more emphatic in praising your committee for doing an effective job of publicizing the potential for trouble. Even if none of the recombinant circles made to date are pathogens or tumorigens, it is only a matter of time until this occurs. Having raised the level of consciousness of the scientific community, however, I would put as much trust in a molecular biologist as in a virologist, for both are subject to similar pressures.

The possibility that you mentioned of making part of the old Camp Dietrick facility available for producing large cultures of plasmid or virus-containing cells under containment is a felicitous one. What a delightful turn-around if the billions poured into that place should eventually have a worthwhile humantarian result! If I were growing a hundred liters of something risky I would certainly like to be able to treat it like the typhoid bacillus (if it stayed inside) or dengue fever virus (if it came out wearing a protein coat). For one liter, however, I might take the risk in my own laboratory. People are purifying things at this scale, doing gradient centrifugations, electrophoresing the proteins and nucleic acids, etc., working with agents that no one wants to see released anywhere on the face of the earth. If we feel the need we can learn these procedures, plus the safety controls to assure ourselves that we are doing them right, in a short time.

Now, who should decide when these measures need to be employed and when they are wasteful and superfluous? You probably wouldn't suggest any special precautions if I were to put the tryptophan synthetase genes from another non-pathogenic species into the Col El plasmid of dear old E. coli K12. You probably would suggest the most stringent precautions if I were to take any portion of EB virus DNA and put it there. Aren't most experiments going to fall in one or the other of these obvious categories? Why can't I or any other experimenter be relied upon to make the decision, just as I'm allowed to decide whether to autoclave my discarded plates and plug my pipettes when introducing a new bacterium into the laboratory?

If we can avoid "permission panels", I say we should do it. Why not set up a single, temporary "advisory panel" instead, to answer any questions about risks for those contemplating experiments in a grey area (polyoma virus + Col E1, for example), to help provide information about containment and sterilization for those who must work in the red area, but not to be concerned about those who deem their projects to be safe? One thing I begin to see after twenty years of exposure to medical men is that the more regulations you impose from above to prevent shady behavior, the more ingenuity will appear from below to evade these monitoring systems. Let us start out, at least, on the premise that scientists will make rational decisions and seek available help when it is in their own best interest to do so.

So now how do we stand, Paul? Have I come half-way around the circle from my original "don't regulate anyone" position? Perhaps. It would not be cheap to set up an NIH or contract lab to answer some of the open questions concerning "risks", to refurbish containment facilities at Camp Dietrick or elsewhere for making and concentrating important but dangerous agents, and to provide a "hot-line" of sorts for worried and concerned scientists. I can see my own next application to NIH falling below the cut-off line because of a diversion of funds for this kind of operation, but it involves a lot less money and time than setting up "permission panels" all over the country. It seems permissable to me to take the cheaper way because the nature of the problem resembles the study of pathogens more than the use of human subjects in research. What we have going for us is the basic decency and caution of the average scientist, plus the enormous resiliency of living things in response to challenges when and if something goes wrong--as it may under any system that is set up.

That, for what it's worth, is my opinion after many hours of thought and discussion. I'll now sit back, shut up, and see what happens.

With best regards,

Irving

Irving P. Crawford, M.D.